SM.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/923,515	08/07/2001	Rosanne M. Crooke	ISPH-0595	1714

36441 7590 03/09/2004

MARY E. BAK
HOWSON AND HOWSON, SPRING HOUSE CORPORATE CENTER
BOX 457
SPRING HOUSE, PA 19477

EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

S.M.

Office Action Summary	Application No.	Applicant(s)	
	09/923,515	CROOKE ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, and 4-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 9/15/03
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicants Arguments and Remarks, filed September 15, 2003 and September 29, 2003.

Claims 3 and 16-20 have been canceled. Claim 11 has been amended. Claims 1, 2, and 4-15 are pending in the instant application.

Claims 1, 2, and 4-15 have been examined on the merits.

Change in Power of Attorney

Applicant's change in Power of Attorney, filed April 14, 2003 is acknowledged.

Information Disclosure Statement

Applicant's information disclosure statement, filed September 15, 2003 is acknowledged. The information referred to therein has been considered on the merits.

Claim Rejections - 35 USC § 112

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 11, 12 and 13 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This rejection is withdrawn** in view of the Examiner's

reconsideration of the claims and the Examiner's decision that one of ordinary skill in the art would be reasonably apprised of the term "compound".

It is noted that in response to this rejection, Applicants argue that the term "compound" has been replaced with the term "oligonucleotide" and thus, this rejection may be properly withdrawn. However, after reviewing the claims, it is noted that the term "compound" has not been replaced with the term "oligonucleotide". Therefore, this rejection is withdrawn in view of the Examiner's reconsideration of the claims, and not Applicants arguments filed September 15, 2003.

Claims 1, 2, 4-10 and 14 were rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection is withdrawn** in view of Applicants arguments and Applicants amendment to the claims to include SEQ ID NO:3 and human apolipoprotein (a), filed September 15, 2003.

Claim 15 was rejected under 35 U.S.C. 112, first paragraph, because specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. **This rejection is withdrawn** in view of Applicants amendment to the claims to recite, "a method of inhibiting the expression of human apolipoprotein (a) in cells or tissues comprising contacting

said cells or tissues *in vitro* with an antisense compound targeted to human apolipoprotein (a) SEQ ID NO:3)."

Claim Rejections - 35 USC § 102

Claims 1, 11, 12, and 15 were rejected under 35 USC 102(b) as being anticipated by Morishita et al. (Circulation, 1998 Vol. 98:1898-1904). **This rejection is maintained** for the reasons of record set forth in the previous office action, filed March 19, 2003. **It is noted that after careful reconsideration of the claims, claims 2 and 14 have been included in this rejection.**

Claim 1 is drawn to a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding human apolipoprotein (a); wherein said compound specifically hybridizes with said nucleic acid molecule encoding human apolipoprotein (a) and inhibits the expression of human apolipoprotein. Claim 2 is dependent on claim 1, and includes all the limitations of claim 1, with the further limitation, wherein the compound is an antisense oligonucleotide. Claims 11 and 12 are drawn to a compound 8 to 50 nucleobases in length that specifically hybridizes with at least an 8-nucleobase portion of an active site on a nucleic acid encoding human apolipoprotein (a). Claim 15 is drawn to a method of inhibiting the expression of human apolipoprotein (a) in cells using a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding human apolipoprotein (a). Claim 14 is dependent on claim 12, and includes all the limitations of claim 12, with the further limitation, wherein the compound is an antisense oligonucleotide.

Morishita et al. disclose three phosphorothioate backbone ribozyme oligonucleotides, 42-base pairs in length targeted to kringle 4 of the human apolipoprotein (a) (see page 1899, Methods and Figure 1A) (Note, the disclosed human apolipoprotein (a) phosphorothioate backbone ribozyme oligonucleotides of Morishita et al. are 80% homologous to the plasminogen gene (see page 1900, last paragraph)). Morishita et al. also disclose that the expression of ribozymes targeting human apolipoprotein (a) inhibited human apolipoprotein (a) protein expression in HepG2 cells (see Figures 2A and 2B), but not plasminogen concentrations (see Figure 3A). Morishita et al. further disclose that ribozyme inhibition of human apolipoprotein abolished the mitogenic action of conditioned medium in HepG2 cells.

Therefore, Morishita et al. anticipate the current invention.

In response to this rejection, Applicants argue that the claims, as now amended, recite that the compounds are *antisense compounds* and thus, excludes the *ribozyme sequence* of Morishita et al.

Applicants arguments have been fully considered, but are not found persuasive because the instant specification at page 11, line 35 discloses, "Antisense compounds include ribozymes". Furthermore, the ribozyme sequence of Morishita et al. meets all the structural requirements of the instant claims and is therefore an inherent antisense compound, absent evidence to the contrary.

Therefore, Morishita et al. anticipate claims 1, 2, 11, 12, 14, and 15.

Claim Rejections - 35 USC § 103

Claims 1, 2, 4, 5, 6-10 and 12-14 were rejected under 35 U.S.C. 103(a) as being unpatentable over Morishita et al. (Circulation, 1998 Vol. 98:1898-1904) in view of Baracchini et al. [U.S. Patent No. 5801154] and Fritz et al. (Journal of Colloid and Interface Science, 1997 Vol. 195:272-288). **This rejection is maintained** for the reasons of record set forth in the previous office action, filed March 19, 2003.

In response to this rejection, Applicants argue that the claims, as now amended, recite that the compounds are *antisense compounds* and thus, excludes the *ribozyme sequence* of Morishita et al. Applicants argue that Morishita et al. do not teach anything specific about antisense sequences to Apo(a), and does not teach or suggest specific antisense sequences that hybridize to Apo (a). Applicants argue that Morishita et al. actually teach away from the concept of antisense sequences to Apo(a) as having any use. Applicants point the Examiner to page 1898 and 1899. Applicants further argue that the two secondary documents teach nothing regarding human apolipoprotein (a) or antisense sequences capable of inhibiting human apolipoprotein (a) activity. Applicants argue that Baracchini refers to antisense compounds that modulate an unrelated protein to human apolipoprotein (a) and Fritz refers to cationic nanoparticles as a carrier system for antisense nucleotides in general. Applicants argue that the references do not teach or suggest any antisense sequences to human apolipoprotein (a) and the combination of Morishita et al. with Baracchini et al. nor Fritz et al. provide any suggestion for antisense sequences targeted to human apolipoprotein (a). Applicants argue that neither Fritz et al. nor Baracchini et al. teaches or suggest a utility for antisense compounds that bind human apolipoprotein (a) and Morishita et al. speculates that there is no utility.

Applicant's arguments have been fully considered, but are not found persuasive. First, Applicants argue that Morishita et al. do not teach anything specific about antisense sequences to Apo(a), and does not teach or suggest specific antisense sequences that hybridize to Apo (a). This is not found persuasive because referring to Applicants disclosure, at page 11, line 35 discloses, "Antisense compounds include ribozymes". Furthermore, the ribozyme sequence of Morishita et al. meets all the structural requirements of the instant claims and is therefore an inherent antisense compound, absent evidence to the contrary. Therefore, Morishita et al. explicitly teach and suggest specific antisense sequences that hybridize to Apo (a). Second, Applicants argue that Morishita et al. actually teach away from the concept of antisense sequences to Apo(a) as having any use. Applicants point the Examiner to page 1898 and 1899. This is not found persuasive because the context for which Morishita et al. teach away from the concept of antisense sequences to Apo(a) as having any use, is in regard to using an antisense strategy to decrease apolipoprotein (a) expression separate from plasminogen because the two share a high degree of homology. Morishita et al. make this point clear by teaching, "it appears to be very difficult to use the antisense strategy to decrease apolipoprotein (a) separate from plasminogen because the structure of the apolipoprotein (a) gene has a very high degree of homology to the plasminogen gene". Therefore, it appears that the Applicant has taken this teaching out of context as Morishita et al. are mostly interested in a novel strategy to *selectively* inhibit apolipoprotein (a) gene expression *apart from* plasminogen. Regarding Applicants arguments that the two secondary documents teach nothing regarding human apolipoprotein (a) or antisense sequences capable of inhibiting human apolipoprotein (a) activity, Applicant argues against the references individually, but must consider the rejection based upon the combination

of the references. *See*, MPEP 2145. While Baracchini et al. and Fritz et al. do not teach or suggest any antisense sequences to human apolipoprotein (a), as argued in the previous Office Action, one of ordinary skill in the art would have been motivated to modify the phosphorothioate ribozyme of Morishita et al. since the prior art has taught the desirability of such modified oligonucleotides are often preferred over native forms because of enhanced cellular uptake, enhanced affinity for nucleic acid target, increased stability in the presence of nucleases and the exhibition of high colloidal stability with low toxic side effects as required for biological experiments (see Baracchini et al., column 3, lines 17-41, column 6, line 37 and Table I and Fritz et al. page 287, last paragraph).

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

After careful reconsideration of the claims, Applicants amendment necessitated the new grounds of rejection presented below.

Claim Objections

Claim 1 is objected to because of the following informalities: Claim 1 recites the term "human apolipprotein (a)". It appears that the term "human apolipprotein (a)" has a typographical error as the instant specification refers to "human apolipoprotein (a)". Correction is required.

Conclusions

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (571) 272-0758. The examiner can normally be reached on M-F 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tcg
February 25, 2004

KAREN A. LACOURCIERE, PH.D
PRIMARY EXAMINER